Synopsis Submitted to

Swami Ramanand Teerth Marathwada University, Nanded

On the topic

EXPLORING ANTICANCER ACTIVITY OF BLUMEA SPECIES

For the degree of

Doctor of Philosophy in Biotechnology

Under the faculty of science

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2025

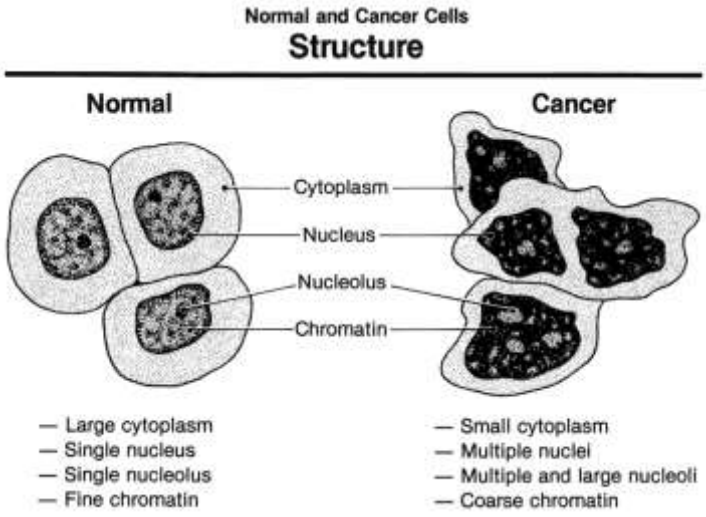
EXPLORING ANTICANCER ACTIVITY OF BLUMEA SPECIES

1- Introduction

Cancer: It is considered one of the leading causes of fatality worldwide and a major barrier to extending the life span. (Chavda V. P et al ., 2023). Cancer is a major public health concern. Over 52,900 individuals are diagnosed with cancer daily, and more than 27,000 people lose their lives due to this disease. It is estimated that by 2040 there will be 28 million new cases and 16.2 million deaths worldwide.(Liu, B et al., 2024). Current biological mechanisms of cancer suggest that all cancers are originated from both environment and genetics. meaning that there are multiple external factors combined with internal genetic changes will lead to human cancer.(Parsa, N. 2012).

Cancer definition: Cancer is essentially disease of the genome which evolves and progresses with accumulations of somatic mutations including copy number alterations (CNA) and structural variants (SV) and epigenomic alterations with and without some hereditability.(Nakagawa, H., & Fujita, M. 2018).

Cancer treatment requires a versatile approach involving a range of strategies aimed at targeting the disease at different levels of conventional therapies, such as surgery, chemotherapy, and radiotherapy. The remaining primary options are applied either alone or in combination depending on the type and stage of the cancer. (Papadaki, E et al., 2024).



Phytochemicals:

Phytoconstituents are non-nutrient chemical compounds that occur naturally in plants and are responsible for color and other organoleptic properties, as well as plant protection. Plants are valuable sources of medicinal products, with a broad spectrum of biological activities. Nearly 25 to 50% of the present pharmaceuticals are derived from plant-by-products. (Tamanna, C. & Ahmed, C. S. A. R. 2023).

The main phytochemical components of medicinal plants are tannins, alkaloids, saponins, cardiac glycosides, steroids, terpenoids, flavonoids, phlobatannins, anthraquinones, and reducing sugars. As proposed by the WHO, the primary health care of most populations in developing countries depends on traditional medicines and mostly natural plant products.

The most important components of the medicinal plant were isolated by extraction using the appropriate solvent. There are different extraction solvents, such as ethanol, methanol, chloroform, acetone, hexane, petroleum ether, ethyl acetate, and aqueous (water). Were used to the phytochemical composition of plant species.(Agidew, M. G. 2022).

Phytochemical screening of plant extracts

This is of paramount importance because of the benefits it offers in various sectors. These screenings were crucial for several reasons. Phytochemical screening aids in the discovery and identification of bioactive compounds in plants that have the potential to be used for medicinal purposes. Many pharmaceutical drugs have their origins in plant-based compounds, making this screening vital for drug development. Second, they play a significant role in the field of nutrition and health. The identification of phytochemicals, such as flavonoids, carotenoids, and polyphenols, in plant extracts helps in understanding their health-promoting properties. These compounds have antioxidant, anti-inflammatory, and anticancer effects, making them valuable for dietary and nutritional purposes.

Phytochemical screening has contributed to the field of traditional medicine and alternative therapies. Traditional herbal remedies often rely on the use of plant extracts, and screening helps validate their efficacy and safety. (Abilkassymova, A et al,.2024).

Medicinal plants:

Medicinal plants are considered potential sources for drug development, and many novel products have been tested in clinical trials. Scientists are investigating the properties of medicinal plants from natural products to develop novel drugs against diseases, such as cancer. Medicinal herbs have a profound scope and have been used to identify potential anticancer compounds (Bhandari et al., 2017).

Herbs or Botanical plants are considered God's gifts to human beings in the form of natural medicines. Among the 21,000 medicinal plants listed by the World Health Organization (WHO) 2500 species are native to India, which stands first in the production of medicinal herbs.

Natural dietary agents, including fruits, vegetables, and spices, have drawn a great deal of attention from both the scientific community and the general public, owing to their ability to suppress cancer. (Shukla et al.,2018).

MEDICINAL PLANTS AND CANCER:

The anticancer properties of medicinal plants depend on their properties; the plants contain several compounds (known as lignads) that have led to the development of drugs.

According to current data, the plant kingdom contains nearly 250,000 plant species, of which only about 10% have been studied and discovered for the treatment of many diseases.

Therefore, the phytochemical properties of different plants and their derived bioactive analogs occur in assorted portions of plants, such as flowers, seeds, stems, bark, fruits, leaves, and embryos, and all these medicinal plants are eminent to yield numerous bioactive metabolites with various pharmacological attributes, including antidiabetic, antiosteoporotic, antimicrobial, hepatoprotective, anti-inflammatory, antimalarial, antiaging, immunomodulatory, antioxidant, antihypertensive, anticancer, and others (Siddiqui et al. .,2022).

The plant collection for finding anticancer agents ended in 1982, but in 1986, the generation of new screening strategies led to the amelioration of plants and the collection of other organisms, mainly focused on the subtropical and tropical zones of the world. Hartwell listed more than 3000 plant have anticancer activity.(Asma, S. Tet al., 2022).

Blumea speices:

Blumea is an annual herb with a strong odor, turpentine, distributed throughout the plain of northwest India up to an altitude of 2,000 m. Few species of this genus have been found in Australia. Most Blumea species are found in various ruderal and strongly secondary habitats such as roadsides and fields.

The Blumea stem is a hairy or glandular herb that is erect, ash-colored, simple or branched, very leafy and 1-2 ft. in height. The leaves are oblate or oblanceolate 5-12 cm long 2-6 cm wide, and have a smaller top. Blumea (Family Asteraceae), commonly known as Jungli muli

and kukraundha, is a common Rabi weed in India. The blumea leaf beetle (Chrysolina madrasae Jackoby) is the main insect pest of this weed. In Ayurveda, blumea is described as bitter, astringent, acrid, thermogenic, errhine, anti-inflammatory, styptic, ophthalmic, digestive, anthelmintic, liver tonic, expectorant, febrifuge, antipyretic, diuretic, deobstruent, and stimulant. Essential oil extracted from the leaves has analgesic, hypothermic, and sedative properties. (Moid, H et al.,2023).

***Blumea oxyodonta*:**

Blumea oxyodonta (Asteraceae) was identified by Dr. Milind Sardesai (SPPU, Pune).

It is a diffuse herb that grows to 30 cm in length. Many stems branch from the base and spread, procumbent, or ascending. Villous white with long glandular hairs. The leaves are radical, clustered at the base, densely silky white, and have glandular hairs on both surfaces.

B. oxyodonta is grown as a weed near moist places of the Ghats and distributed throughout India, Myanmar, Pakistan, China, Vietnam and the Philippines In the traditional system of medicine the decoction of the roots is used for treatment of impotency and spermatorrhea.

Phytochemical Composition

Blumea oxyodonta is rich in terpenoids, with a study identifying 61 compounds in its essential oil. The main constituents include β-caryophyllene (23.5%) 2,5-dimethoxy-p-cymene (14.7%) and germacrene D (13.2%)The plant's essential oil is predominantly composed of sesquiterpene hydrocarbons (45.8%) and oxygenated sesquiterpenes (25.8%) .(Joshi, 2018).

Literature Review

Alabi, M. A et .al.,(2023) In this study *Trigonella foenum-graecum* seed methanolic extract shows promise as a breast cancer treatment due to its ability to induce cell death (apoptosis or necrosis), disrupt cell membrane function, and increase reactive oxygen species in MCF-7 breast cancer cells. These findings suggest its potential as a therapeutic agent and encourage further research, especially regarding the optimal dosages. Previous research supports these conclusions, highlighting the importance of continued investigation of *T. foenum-graecum* extract for cancer therapy.

Aziz, I. M et.al.,(2024) This study analyzed the essential oil of Alpinia galanga (AgRE) using gas chromatography-mass spectrometry (GC-MS) and found it to be a rich source of β-

turmerone and α-turmerone. Consistent with previous studies, AgRE exhibited strong cytotoxic, antibacterial, and antioxidant properties, potentially reducing the risk of complex diseases. Additionally, AgRE selectively induced apoptosis in the MCF-7 and HepG2 cancer cell lines. These findings suggest that A. galanga could be a valuable natural product for the pharmaceutical industry. However, further studies are needed to elucidate the mechanisms underlying the antioxidant and antibacterial effects of AgRE and to explore its potential against infectious diseases and cancer through additional in vitro and in vivo research.

Ameur**, S et.al.,(2024)**This study is the first to investigate the chemical composition and potential biological activities of *Cistus libanotis* from Algeria, identifying key compounds in its essential oils, including γ-terpinene, camphene, α-phellandrene, and 4-carene. Analysis of the ethanolic extract revealed 24 components, with shikimic acid being the most abundant, and the plant extracts exhibited promising antiproliferative activity. These findings provide a solid foundation for future research on the medicinal potential, therapeutic mechanisms, and possible synergistic effects of *C. libanotis* in promoting human health.

Perumal et al. (2021) demonstrated that rambutan endocarp extracts, particularly methanol extract, exhibit potent anticancer effects against human hepatocellular carcinoma (HepG-2) cells. The anticancer and apoptotic properties appeared to be primarily due to the presence of major polyphenolic compounds, specifically phenols and flavonoids, in the methanol extract. Future research should focus on isolating the active compounds from the rambutan methanol endocarp extract and evaluating their potential as anticancer agents.

Malar, T. J et.al., (2020) A study analyzing Azadirachta indica A. Juss and Melia azedarach Linn revealed their rich phytochemical composition including steroids, alkaloids, phenols, flavonoids, saponins, tannins, anthraquinone, and amino acids, with A. indica showing strong activity against K. pneumonia while M. azedarach was effective against S. aureus. These medicinal plants have demonstrated potential as both natural antibacterial and anticancer agents, making them valuable for therapeutic applications.

Rasheed, H. M.et.al.,(2022) In this research, phytochemical analysis of D. ramosa using tandem high-resolution mass spectrometry revealed 18 compounds in the crude extract and its fractions, primarily consisting of flavonoids and phenolic acids. The D. ramosa extract and fractions demonstrated significant cytotoxic effects against liver cancer cells and mild effects on prostate cancer cell lines, while remaining safe for non-cancerous cells. These findings

suggest that D. ramosa has promising antitumor potential and could be a valuable source of safe anticancer drugs.

Krishnakumar, A. K et.al.,(2024)studied through molecular docking analysis, twenty-nine active phytochemicals from common Indian spices were evaluated for their potential to combat breast cancer invasion and bone metastasis by targeting BCL3 and CXCL10 proteins, with sesamolin from sesame and piperine from pepper showing particularly strong binding affinities. Although experimental validation is required to confirm their efficacy and safety, the promising drug-likeness properties of these phytochemicals support their therapeutic potential. Future research directions include comprehensive in vitro and in vivo studies, including dosage optimization, delivery methods, potential synergistic effects with existing treatments, and thorough safety assessments prior to clinical application.

Ohiagu, F. O et.al.,(2021) This literature review highlights 51 Nigerian medicinal plants demonstrating anticancer activity across various cancers, attributed to bioactive compounds like polyphenols and alkaloids that induce antiproliferative and apoptotic effects. Notably, 14 anticancer drugs derived from these plants, including paclitaxel and vincristine, have undergone clinical trials, emphasizing their potential for future drug development. This review recommends further research focusing on leaf, root, and stem bark extracts, which are the primary sources of these anticancer compounds, to harness the plants for accessible and affordable cancer treatments.

Objectives of Research:

1-Selection and collection of plants.

2-Extraction and purification.

3-Characterization of the compounds.

4-Anticancer activity.

Methods And Materials

Healthy plant parts were collected for research purposes.(leaves of Blumea oxyodonta) in the running season 2023. The plant samples were washed with tap water to remove the soil and

then cut into small pieces, shade dried and made fine powder and store in air tight container for further use

Extraction: Ethanol was used for extraction using a Soxhlet apparatus.

The temperature maintained during each extraction was 10-20^{0}c lower than the melting point of the respective solvents used. The extraction procedure was fixed, that is, 50 g of sample was mixed for 6 h in 500 ml of solvent (Kulkarni and Kamble 2021).

Extraction and Spectral analysis (HR- LCMS)
Isolation and spectral characterization of bioactive compounds.
SAR using Pass analysis for bioactive compounds

Active compounds:

- Morindone
- Dihydrodeoxystreptomycin
- 3-tert-Butyl-5-methylcatechol
- 19-Noretiocholanolone
- Harderoporphyrin
- Protorifamycin I
- Endomorphin-2
- Pheophorbide a
- Euphornin
- Hypaconitine
- Harderoporphyrinogen

Steps of the analysis of compounds

1-Download structure from PDB
2-Download ligand that is attached with structure from Pubchem
3-Convert it into pdb using PyMol
4- Go on USCF chimera and prepare protein
5- Find active site from protein plus server
6- Add ligand through open babel , energy minimize it and convert in to pdb.qt
7- Select ligands and macromolecule (target)
8- Click forward
9- Select grid box

10- Adjust grid box

11- Start docking

Target:

The target which used: MDM2-p53 (PDB ID:4HG7) and KRAS (PDB ID: 5OCT)

Result

Assessment of amino acids involved in the interaction:

Following amino acids are involved in the interaction with different targets selected for the study:

Active site of amino acids in the 4hg7 target

LE_19_A,LEU_54_A,PHE_55_A,LEU_57_A,GLY_58_A,LN_59_A,ILE_61_A,MET_62_A,LEU_66_A,TYR_67_A,ASP_68_A,GLN_71_A,GLN_72_A,HIS_73_A,ILE_74_A,VAL_75_A,LEU_82_A,PHE_86_A,PHE_91_A,SER_92_A,VAL_93_A,LYS_94_A,GLU_95_A,HIS_96_A,ARG_97_A,ILE_99_A,TYR_100_A,ILE_103_A.

Active site of amino acids in the 5octa target

HIS_61_A, ARG_68_A , LYS_88_A ,ASP_92_A,ILE_93_A, HIS_95_A TYR_96_A, ARG_97_A, GLN_99_A.

Active site of amino acid in the 5octb target:

GLU_3_B,TYR_4_B,LYS_5_B,LEU_6_B,VAL_7_B,GLU_37,ASP_38_B SER_39_B,TYR_40_B,ARG_41_B,ASP_54_B,ILE_55_B,LEU_56_B,GLN_70_B,TYR_71_B,MET_72_B,ARG_73_B,THR_74_B,GLY_75_B,GLU_76_B,GLU_3_E,ARG_41_E.

Active site of amino acids in the 5octc target

GLU_3_C,TYR_4_C,LYS_5_C,LEU_6_C,VAL_7_C,SER_39_C,TYR_40_C,ARG_41_C,ASP_54_C,ILE_55_C,LEU_56_CGLN_70_C,TYR_71_C,MET_72_C,ARG_73_C,THR_74_C,GLY_75_C,GLU_76_C.

Active site of amino acid in the 5octd target:

GLU_3_D,TYR_4_D,LYS_5_D,LEU_6_D,VAL_7_D,GLU_37_D,ASP_38_D,SER_39_D,TYR_40_D,ARG_41_D,ASP_54_D,ILE_55_DLEU_56_D,GLN_70_DTYR_71_D,MET_72_D,ARG_73_D,THR_74_D,GLY_75_D,GLU_76_D,GLU_3_F.

Active site of amino acids in the 5octe target

TYR_4_E,LYS_5_E,LEU_6_E,VAL_7_E,GLU_37_E,ASP_38_E,SER_39_ETYR_40_E,ARG_41_E,ASP_54_E,ILE_55_E,LEU_56_E,GLN_70_ETYR_71_EMET_72_E,ARG_73_E,THR_74_E,GLY_75_E,GLU_76_E.

Active site of amino acids in the 5octf target

GLU_3_D,GLU_3_F,TYR_4_F,LYS_5_F,VAL_7_F,GLU_37_F,ASP_38_FSER_39_F,TYR_40_F,ARG_41_F,ASP_54_F,ILE_55_F,LEU_56_F,GLN_70_F,TYR_71_F,MET_72_F,ARG_73_F,THR_74_FGLY_75_F,GLU_76_F,GLY_77_F,PHE_78_F.

Sr. No	**Molecule**	**Binding affinity in kcal/mol**
1	Morindone	-7.1
2	Dihydrodeoxystreptomycin	-5.6
3	3-tert-Butyl-5-methylcatechol	-5.3
4	19-Noretiocholanolone	-7.6
5	Harderoporphyrin	-7.7
6	Protorifamycin I	-7.7
7	Endomorphin-2	-7.6
8	Pheophorbide a	-8.3
9	Euphornin	-7.5
10	Hypaconitine	-7.1
11	Harderoporphyrinogen	-7.1
12	nut(reference ligand)	-8

Table 1: Binding affinity for selected ligands with comparison to reference molecule with 4hg7 target

Sr.No	**Molecule**	**Binding affinity in kcal/mol**
1	Morindone	-6.4
2	Dihydrodeoxystreptomycin	-5.5
3	3-tert-Butyl-5-methylcatechol	-5.3
4	19-Noretiocholanolone	-6.7
5	Harderoporphyrin	-6.5
6	Protorifamycin I	-7.3
7	Endomorphin-2	-7.2
8	Pheophorbide a	-6.9
9	Euphornin	-7.2
10	Hypaconitine	-6.1
11	Harderoporphyrinogen	-6.7
12	**9R5(reference ligand)**	-5.2

Table 2:Binding affinity for selected ligands with comparison to reference molecule with 5octa target

Sr. No	**Molecule**	**Binding affinity in kcal/mol**
1	Morindone	-7.5
2	Dihydrodeoxystreptomycin	-5.3
3	3-tert-Butyl-5-methylcatechol	-5.4
4	19-Noretiocholanolone	-6.4
5	Harderoporphyrin	-6.1
6	Protorifamycin I	-6.9
7	Endomorphin-2	-6.7
8	Pheophorbide a	-6.7
9	Euphornin	-7.1
10	Hypaconitine	-6.1
11	Harderoporphyrinogen	-7.4
12	**9R5(reference ligand)**	-5.2

Table3. Binding affinity for selected ligands with comparison to reference molecule with 5octb target

Sr. No	**Molecule**	**Binding affinity in kcal/mol**
1	Morindone	-7.2
2	Dihydrodeoxystreptomycin	-5.6
3	3-tert-Butyl-5-methylcatechol	-5.4
4	19-Noretiocholanolone	-6.7
5	Harderoporphyrin	-7
6	Protorifamycin I	-7
7	Endomorphin-2	-6.5
8	Pheophorbide a	-6.9
9	Euphornin	-6.2
10	Hypaconitine	-6.2
11	Harderoporphyrinogen	-7.5
12	**9R5(reference ligand)**	-5.2

Table4. Binding affinity for selected ligands with comparison to reference molecule with 5octc target

Sr.No	Molecule	Binding affinity in kcal/mol
1	Morindone	-7.6
2	Dihydrodeoxystreptomycin	-6.1
3	3-tert-Butyl-5-methylcatechol	-5.4
4	19-Noretiocholanolone	-6.3
5	Harderoporphyrin	-6.6
6	Protorifamycin I	-7.4
7	Endomorphin-2	-6.4
8	Pheophorbide a	-6.3
9	Euphornin	-6.7
10	Hypaconitine	-5.6
11	Harderoporphyrinogen	-7.1
12	9R5(reference ligand)	-5.2

Table5: Binding affinity for selected ligands with comparison to reference molecule with 5octd target

Sr. No	Molecule	Binding affinity in kcal/mol
1	Morindone	-7.5
2	Dihydrodeoxystreptomycin	-5.4
3	3-tert-Butyl-5-methylcatechol	-5.5
4	19-Noretiocholanolone	-6.3
5	Harderoporphyrin	-6.6
6	Protorifamycin I	-6.8
7	Endomorphin-2	-6.9
8	Pheophorbide a	-6.8
9	Euphornin	-6.7
10	Hypaconitine	-6
11	Harderoporphyrinogen	7.1
12	9R5(reference ligand)	-5.1

Table 6: Binding affinity for selected ligands with comparison to reference molecule with 5octe target

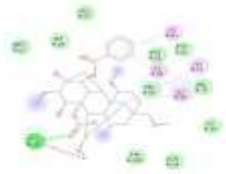
Sr.No	Molecule	Binding affinity in kcal/mol
1	Morindone	-7.5
2	Dihydrodeoxystreptomycin	-5.3
3	3-tert-Butyl-5-methylcatechol	-5.9
4	19-Noretiocholanolone	-6.4
5	Harderoporphyrin	-6.6
6	Protorifamycin I	-6.9
7	Endomorphin-2	-6.6
8	Pheophorbide a	-6.7
9	Euphornin	-6.8
10	Hypaconitine	-5.9
11	Harderoporphyrinogen	-7.6
12	9R5(reference ligand)	-5.7

Table7: Binding affinity for selected ligands with comparison to reference molecule with 5octf target

4hg7 and Euphornin complex

4hg7 and Endomorphin-2 complex

4hg7 and Dihydrodeoxystreptomycin complex



4hg7 and Hypaconitine complex

4hg7 and Harderoporphyrinogen complex

4hg7 and Harderoporphyrin complex

4hg7 and nut complex

4hg7 and Morindone complex

4hg7 and Protorifamycin I complex

4hg7 and Pheophorbide a complex

Docking images of 4hg7 target with compounds

4hg7 and Dihydrodeoxystreptomycin complex

4hg7 and 3-tert-Butyl-5-methylcatechol complex

4hg7 and 19-Noretiocholanolone complex

4hg7 and Endomorphin-2 complex

4hg7 and Harderoporphyrinogen complex

4hg7 and Harderoporphyrin complex

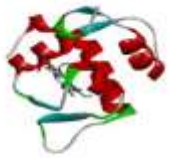
4hg7 and Euphornin complex

4hg7 and nut complex

4hg7 and Morindone complex

4hg7 and Hypaconitine complex

4hg7 and Protorifamycin I complex



4hg7 and Pheophorbide a complex

2D diagram
5octa target with compounds

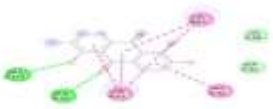
5octa and Hypaconitine complex

5octa and Harderoporphyrinogen complex

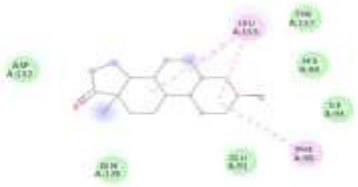
5octa and Harderoporphyrin complex

5octa and Protorifamycin I complex

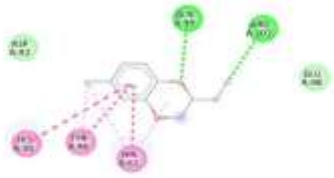
5octa and Pheophorbide a complex



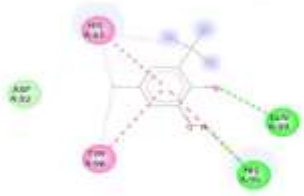
5octa and Morindone complex



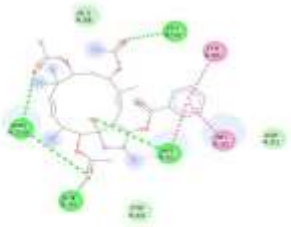
Socta and 19-Noretiocholanolone complex



Socta and 9r5 complex

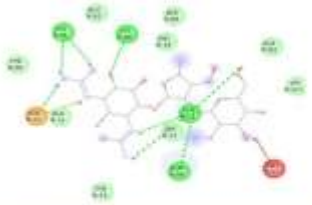


Socta and 3-tert-Butyl-5-methylcatechol complex



Socta and Euphornin complex

Socta and Endomorphin-2 complex



Socta and Dihydrodeoxystreptomycin complex

Docking images
Socta target with compounds

Socta and 19-Noretiocholanolone complex

Socta and 9r5 complex

Socta and 3-tert-Butyl-5-methylcatechol complex

Socta and Euphornin complex

Socta and Endomorphin-2 complex

Socta and Dihydrodeoxystreptomycin complex

Socta and Hypaconitine complex

Socta and Harderoporphyrinogen complex

Socta and Harderoporphyrin complex

Socta and Protorifamycin I complex

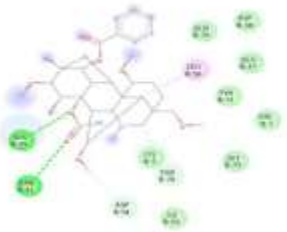
Socta and Pheophorbide a complex

Socta and Morindone complex

2D diagram
5octb target with compounds

5octb and Pheophorbide a complex

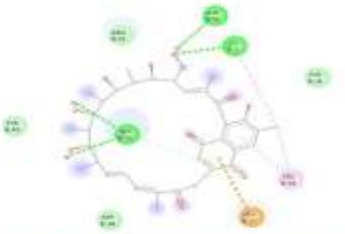
5octb and Morindone complex



5octb and Hypaconitine complex

5octb and Euphornin complex

5octb and9r5 complex



5octb and Protorifamycin I complex

5octb and 3-tert-Butyl-5-methylcatechol complex

5octb and Dihydrodeoxystreptomycin complex

5octb and 19-Noretiocholanolonecomplex

5octb and Harderoporphyrinogen complex

5octb and Harderoporphyrin complex

5octb and Endomorphin-2 complex

Docking images
5octb target with compounds

5octb and Pheophorbide a complex

5cotb and Morindone complex

5octb and Hypaconitine complex

5octb and 9r5 complex

5octb and 3-tert-Butyl-5-methylcatechol complex

5octb and Protorifamycin I complex

5octb and Endomorphin-2 complex

5octb and Dihydrodeoxystreptomycin complex

5octb and 19-Noretiocholanolone complex

5octb and Harderoporphyrinogen complex

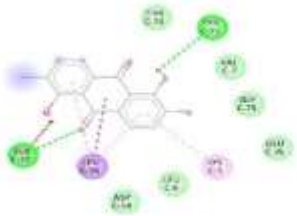
5octb and Harderoporphyrin complex

5octb and Euphornin complex

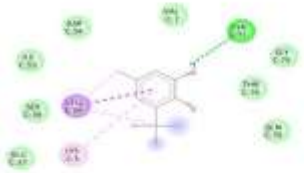
2D diagram
5octc target with compounds

5octc and Pheophorbide a complex

5octc and Hypaconitine complex

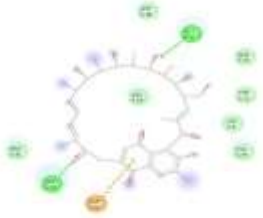


5octc and Morindone complex



5octc and 3-tert-Butyl-5-methylcatechol complex

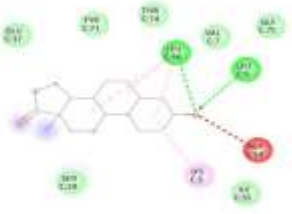
5octc and 9r5 complex



5octc and Protorifamycin I complex

5octc and Endomorphin-2 complex

5octc and Dihydrodeoxystreptomycin complex



5octc and 19-Noretiocholanolone complex

5octc and Harderoporphyrinogen complex

5octc and Harderoporphyrin complex

5octc and Euphornin complex

Molecular Dynamics: Simulation

Name	Total Energy (kcal/mol)
4hg7_with_3-tert-Butyl-5-methylcatechol_complex	-1916.9900
4hg7_with_Dihydrodeoxystreptomycin_complex	-1785.4544
4hg7_with_Endomorphin-2complex	-2041.0572
4hg7_with_Euphornin_complex	-1903.4820
4hg7_with_Harderoporphyrinogen_complex	-1462.8993
4hg7_with_Morindone_complex	-1935.7845
4hg7_with_Protorifamycin_I_complex	-1873.1789
4hg7_with_19-Noretiocholanolone_complex	-1967.0904
4hg7_with_Harderoporphyrin_complex	-2836.393
4hg7_with_Hypaconitine_complex	-3193.254
4hg7_with_Pheophorbide_a_complex	-3269.908
4hg7_with_nut_complex	-1831.8846

Table 1: simulation result of 4hg7 target with compounds

Name	Total Energy (kcal/mol
5oct_a_with_3-tert-Butyl-5-methylcatechol_complex	-5263.1284
5oct_a_with_19-Noretiocholanolone_complex	-5157.8339
5oct_a_with_Dihydrodeoxystreptomycin_complex	-5175.0386
5oct_a_with_Endomorphin-2_complex	-5179.2240
5oct_a_with_Euphornin_complex	-5031.5971
5oct_a_with_Hypaconitine_complex	-5017.4270
5oct_a_with_Morindone_complex	-5367.2419
5oct_a_with_Pheophorbide_a_complex	-4998.6292
5oct_a_with_Protorifamycin_I_complex	-5085.6138
5oct_a_with_Harderoporphyrin_complex	-8304.867
5oct_a_with_Harderoporphyrinogen_complex	-6358.261
5oct_a_with_9r5_complex	-5276.5327

Table 2: simulation result of 5octa target with compounds

Name	Total Energy (kcal/mol)
5oct_b_with_3-tert-Butyl-5-methylcatechol_complex	-8458.057
5oct_b_with_19-Noretiocholanolone_complex	-8244.726
5oct_b_with_Dihydrodeoxystreptomycin_complex	-8400.276
5oct_b_with_Endomorphin-2_complex	-8701.349
5oct_b_with_Euphornin_complex	-8438.149
5oct_b_with_Harderoporphyrin_complex	-1346.491
5oct_b_with_Harderoporphyrinogen_complex	-1054.651
5oct_b_with_Hypaconitine_complex	-8219.713
5oct_b_with_Morindone_complex	-8455.533
5oct_b_with_Pheophorbide_a_complex	-8107.551
5oct_with_Protorifamycin_I_complex	-8357.472
5oct_b_with_9r5_complex	-8442.510

Table 3 : simulation result of 5octb target with compounds

Name	Total Energy (kcal/mol)
5oct_c_with_3-tert-Butyl-5-methylcatechol_complex	-8305.386
5oct_c_with_19-Noretiocholanolone_complex	-8315.203
5oct_c_with_euphornin_complex	-4902.7003
5oct_c_with_Endomorphin-2_complex	-4991.5882
5oct_c_with_Harderoporphyrinogen_complex	-5816.980
5oct_c_with_Hypaconitine	-4778.1411
5oct_c_with_Morindone_complex	-5014.5258
5oct_c_with_Pheophorbide_a__complex	-4733.8299
5oct_c_with_Protorifamycin_I	-4855.5987
5oct_c_with_Harderoporphyrin_complex	-6018.557
5oct_c_with_Dihydrodeoxystreptomycin_complex	-4286.9070
5oct_c_with 9r5_complex	-4812.1635

Table 4: simulation result of 5octc target with compounds

Name	Total Energy (kcal/mol)
5oct_d_with_3-tert-Butyl-5-methylcatechol_complex	-8276.681
5oct_d_with_19-Noretiocholanolone_complex	-8328.202
5oct_d_with_Dihydrodeoxystreptomycin_complex	-8171.449
5oct_d_with_Endomorphin-2_complex	-6837.3432
5oct_d_with_Euphornin_complex	-8169.555
5oct_d_with_Harderoporphyrin_complex	-7765.061
5oct_d_with_Harderoporphyrinogen_complex	-5975.082
5oct_d_with_Hypaconitine_complex	-4720.9098
5oct_d_with_Morindone_complex	-4891.2770
5oct_d_with_Pheophorbide_a_complex	-4624.7495
5oct_d_with_Protorifamycin_I_complex	-8000.686
5oct_d_with_9r5_complex	-4902.7708

Table 5 : simulation result of 5octd target with compounds

Name	Total Energy (kcal/mol)
5oct_e_with_3-tert-Butyl-5-methylcatechol_complex	-4942.7947
5oct_e_with_19-Noretiocholanolone_complex	-8417.360
5oct_e_with_Dihydrodeoxystreptomycin_complex	-4885.8409
5oct_e_with_Endomorphin-2_complex	-4943.2604
5oct_e_with_Euphornin_complex	-8233.740
5oct_e_with_Harderoporphyrin_complex	-6162.250
5oct_e_with_Harderoporphyrinogen_complex	-5918.252
5oct_e_with_Hypaconitine_complex	-8217.328
5oct_e_with_Morindone_complex	-4957.4908
5oct_e_with_Pheophorbide_a_complex	-4777.7347
5oct_e_with_Protorifamycin_I_complex	-4844.9129
5oct_e_with_9r5_complex	-5002.0225

Table 6: simulation result of 5octe target with compounds

Name	**Total Energy (kcal/mol)**
5oct_f_with_3-tert-Butyl-5-methylcatechol_complex	-5016.7602
5oct_f_with_19-Noretiocholanolone_complex	-8302.769
5oct_f_with_Dihydrodeoxystreptomycin_complex	-8349.139
5oct_f_with_Endomorphin-2_complex	-4945.2315
5oct_f_with_Euphornin_complex	-8373.448
5oct_f_with_Harderoporphyrin_complex	-7894.687
5oct_f_with_Harderoporphyrinogen_complex	-5629.844
5oct_f_with_Hypaconitine_complex	-4759.4127
5oct_f_with_Morindone_complex	-4995.4059
5oct_f_with_Pheophorbide_a complex	-4791.1261
5oct_f_with_Protorifamycin_I_complex	-8181.939
5oct_f_with_9r5_complex	-8452.902

Table 7: simulation result of 5octf target with compounds

Discussion

According to the result we obtained shown in the tables ,in table1 the binding affinity of reference ligand (nut) is -8 as we notice with select compound the are different values of binding affinity with MDM2-p53 (PDB ID:4HG7) target , the highest value is -8.3 in pheophorbide a compound , this lead this compound as better ligand for developing drugs against of MDM2-p53 (PDB ID:4HG7)

In table2 the binding affinity of reference ligand (9R5) is -5.2 and as we notice with select compound there are different values of binding affinity with and KRAS (PDB ID: 5OCTa) target, the highest value is -7.3 in protorifamycin I compound, which led the compound to be a better ligand for developing drugs against KRAS (PDB ID: 5OCTa).

As shown in Table 3, the binding affinity of the reference ligand (9R5) was -5.2, and the highest value was -7.5, which indicated that the compound was a better ligand for developing drugs against KRAS (PDB ID: 5OCTb).

As shown in Table 4, the binding affinity of the reference ligand(9R5) was -5.2, and the highest value is -7.5 of Harderoporphrinogen this lead the compound to be a better ligand for developing drugs against KRAS (PDB ID: 5OCTc).

In table 5 the binding affinity of reference ligand (9R5)is -5.2 and the highest value is -7.6 of Morindone this lead the compound as better ligand for developing drugs against of and KRAS (PDB ID: 5OCTd)

In table 6 the binding affinity of reference ligand (9R5)is -5.1and the highest value is -7.6 of Morindone this lead the compound as better ligand for developing drugs against of and KRAS (PDB ID: 5OCTe)

As shown in Table 7, the binding affinity of the reference ligand (9R5) was -5.1, and the highest value was -7.6, indicating that the compound is a better ligand for developing drugs against KRAS (PDB ID: 5OCTf).

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